The Late Prognostic Value of Acute Scintigraphic Measurement of Myocardial Infarction Size

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SUMMARY Infarct, perfusion and blood pool scintigraphy were performed in 62 patients during hospitalization for acute myocardial infarction. The largest measured infarct or perfusion image defect and left ventricular ejection fraction were related to the late prognosis determined a mean of 16 months after the event.

Breakpoint values for all scintigraphic variables could separate those who were asymptomatic on follow-up from those who died. The best indicators for selection of survivors and nonsurvivors were a scintigraphic infarct size ≥ 25 cm² and a perfusion abnormality ≥ 35% of the projected left ventricular area. Among patients with perfusion abnormalities above this limit, 61% died; 93% of those with small perfusion abnormalities survived. Scintigraphic measurements of relative myocardial perfusion and function best separated patients asymptomatic on follow-up from those who developed heart failure and also best identified those with an unfavorable evolution, who developed heart failure or died. Early scintigraphic parameters appeared more accurate than other clinical laboratory indicators for determining late prognosis and could be important in planning treatment after acute infarction.

ACUTE myocardial infarct (AMI) size is an indicator of prognosis after infarction. Postmortem studies have documented that death during the acute phase is frequently associated with infarcts that involve more than 40% of the left ventricular mass.1 The clinical course of patients after AMI has also been related to historical, clinical and admission laboratory data,2-4 to hemodynamic findings during early hospitalization,5-6 and to the severity of ventricular arrhythmias during the acute phase.7,8 Many of these prognostic indicators are indirectly related to AMI size, and several investigators have shown that left ventricular function, one of the main determinants of morbidity and mortality after AMI,9-11 is related to the extent of myocardial necrosis.12-14 Similarly, peak serum levels of enzymes released during AMI have shown a general correlation with prognosis15,16 and enzymatic determinations of infarct size from serial serum creatine kinase (CK) measurements have been proposed as prognostic indicators.17

A search for simple and accurate indicators of prognosis after AMI has been prompted by the unreliability of clinical findings,18 the invasive nature of hemodynamic measurements, and the lack of reproducibility of enzymatic determinations of infarct size.19 Recently, technetium-99m pyrophosphate (99mTc-PYP) infarct scintigrams and rest thallium-201 (201Tl) myocardial perfusion scintigrams were shown to correlate well with pathologic measurements of acute infarct size in dogs20,21 and in humans.22,23

Several investigators have reported promising results using scintigraphic variables as prognostic indicators of AMI. Rigo et al.24 and Schelbert et al.25 found that a normal scintigraphic left ventricular ejection fraction (LVEF) early after AMI predicted survival. The extent and intensity of the abnormality on infarct scintigraphy have also been correlated with morbidity and mortality after AMI.25,26 Recently, scintigraphic perfusion defect size measured early in patients in Killip class I and II was shown to be the best predictor of early and late mortality in patients with AMI.27

In the current study, we sought to determine the value of scintigraphic indicators of infarct size and left ventricular function in predicting the late clinical course of patients after AMI. For this purpose, a quantitative analysis of 99mTc-PYP infarct scintigrams,21 201Tl perfusion scintigrams, and equilibrium gated blood pool scintigrams was performed during the initial hospitalization in a population of patients admitted with AMI and was correlated with the clinical course of patients during follow-up after hospital discharge.

Methods

Patients

Historical features, including the presence of prior infarction, and electrocardiographic, enzymatic and scintigraphic studies, were evaluated in 62 patients admitted to the coronary care unit with AMI. Fifty-one (82.3%) were males, mean age 69 years (range 52-81 years). The diagnosis of AMI was based on at least two of the following criteria: a history of typical, prolonged

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chest pain; electrocardiographic changes indicative of myocardial injury, including ST depression ≥ 1.0 mm or T-wave inversions persisting for 24 hours or more, a newly developed QS complex, or Q waves ≥ 0.04 second; and characteristic elevation of total CK to a peak level ≥ 90 IU/l and/or MB band component ≥ 4% of the total CK. Serum enzyme determinations were made on admission, then every 4 hours to 24 hours and every 6 hours to 72 hours. CK was measured by an electrophoretic method and CK-MB by a fluorometric method. Historical and electrocardiographic evidence of infarction was sought. Nineteen patients (30.7%) had evidence of one or more previous myocardial infarctions, with a well documented history, prior pathologic Q waves or both.

Transmural myocardial infarction was diagnosed on the basis of the appearance of new QS complexes or Q waves ≥ 0.04 second. Subendocardial infarction was diagnosed on the basis of T-wave inversion or ST-segment depression persisting for 24 hours or more without loss of R-wave voltage, or the development of new Q waves. The location of AMI was determined in all patients using standard ECG criteria.

In addition to the evaluation of the presence and site of AMI and the measurement of enzyme values, each patient was assessed for atrial arrhythmias, including supraventricular tachycardia, atrial fibrillation or flutter, ventricular arrhythmias including ventricular tachycardia and fibrillation, evidence of bundle branch block and atrioventricular block, and for the presence of symptoms or signs of congestive heart failure (CHF). These included orthopnea, dyspnea on exertion, shortness of breath, pulmonary rales, a left ventricular gallop, or radiographic evidence of pulmonary flow redistribution.

Patients were added to the study over a 3-year period. They were excluded if they presented to the coronary care unit later than 24 hours after the onset of the event or if they demonstrated clinical signs of advanced heart failure, shock, or life-threatening arrhythmias that required aggressive medical or surgical therapy and prevented their participation or made them intolerant to the imaging procedures. Studies that were not clinically indicated for patient evaluation were done after the patient gave verbal and written informed consent.

Scintigraphic Studies

Scintigraphic studies were done as soon as possible. All studies were performed during the acute phase of infarction within 10 days of the event, and 88% of all scintigraphic studies, including 55 of 57 infarct scintigrams (96.5%), 38 of 48 perfusion scintigrams (79%), and 48 of 55 blood pool scintigrams (87.3%) were performed within 4 days after the onset of symptoms.

Owing to clinical and technical restraints, only 66% of patients had all three scintigraphic studies; 24% had two studies and 10% had only a perfusion or infarct scintigram. Of the 15 patients who had two studies, nine underwent infarct imaging and radioangiography, and five of the six patients who had only one study underwent infarct scintigraphy.

Myocardial infarct scintigraphy (99mTc-PYP) was never performed earlier than 1 day or later than 7 days after the onset of symptoms; 55 of 57 studies were performed within 4 days of admission. For each study, 15–20 mCi of 99mTc-PYP manufactured according to the method of Huberty and co-workers were administered intravenously and images obtained 2–4 hours later to 300,000 counts in 30° right anterior oblique (RAO), anterior, 45° left anterior oblique (LAO), 60° LAO, and left lateral projections, using a portable Ohio Nuclear series 120 or Searle PhoGamma V scintillation camera with a high-resolution collimator. Focal myocardial abnormalities of intensity grade 2–4+ according to the method of Parkey and co-workers were considered abnormal. The absolute area of abnormal 99mTc-PYP uptake was quantitated by planimetry of the Polaroid photographs in the projection that showed the largest abnormality in each patient. Planimetered areas were expressed in square centimeters by using a conversion factor derived from the ratio between the projected and actual areas of the fields of view.

Myocardial perfusion scintigraphy was performed on the day of the onset of symptoms in 21 patients (44%), in nine within the initial 12 hours. Thallium scintigraphy was performed within 2–4 days after the onset of the acute event in 17 patients (35%) and between the fifth and tenth day in 10 patients (21%).

In each patient, 2 mCi of 201Tl were administered intravenously and scintigraphy was performed 10 minutes later, at rest, using the same scintillation cameras, a low-energy, all-purpose collimator during the initial 20 studies and a high-sensitivity collimator in the remainder. Imaging was performed in each case in the same multiple projections as previously noted where the initial perfusion scintigram was acquired to 300,000 counts and each subsequent projection obtained to isotime. As with quantitation of the infarct scintigram, perfusion abnormalities were quantitated from Polaroid images in the projection showing the largest perfusion abnormality. All Polaroid images were obtained in a standardized manner using 087 film and Vari Back II triple-lens camera, which permits the simultaneous acquisition of three images with varying exposure settings. Associated with the proper display scope intensity, this camera virtually assures the recording of a satisfactory and, in most instances, optimally contrasted image. The variable aperture of the triple-lens camera is adjusted to permit image acquisition with f/8, f/11 and f/16, allowing the camera to cover the large count density sometimes encountered. A neutral-density filter, coded on each lens and matched to the light predicted by the phosphor of the display scope, enhances the optimal capability of the camera and assures a uniformity of image intensities across the field of view. The size of scintigraphic defects was planimetered from the Polaroid photographs of perfusion images, as was the entire projected area of the left ventricular myocardium. By using the field dimension calibration factor noted above, defects on perfusion scintigraphy were expressed in terms of the absolute projected area of abnormality in square centi-
meters and also as the percentage of projected area of the left ventricle. The perfusion image abnormality was also calculated as the average absolute defect size and percentage of projected left ventricular involvement in anterior, LAO 45° and left lateral projections.

Scintigraphic areas outlined manually on the original Polaroid image correlated well with areas planimetered using a mechanical hand-held device (r = 0.92). The two measures showed no significant difference by a one-tailed t test from areas measured on images after a uniform fourfold magnification. Similarly, areas manually outlined from the original Polaroid images and mechanically planimetered showed no significant difference from those planimetered using a computerized measurement applied to these same outlines. The mechanical planimeter was calibrated using marked areas of known dimensions.

The reproducibility of the quantitative analysis of infarct and perfusion scintigrams by the methods outlined above were also tested in 20 random patients. When scintigrams were measured blindly twice at least 1 week apart, the mean absolute intraobserver percentage variation in measurement of the largest projected infarct and perfusion scintigraphic abnormalities were + 4.2% and ± 5.8%, respectively. Expressed similarly, the mean interobserver variation was ± 6.5% for infarct scintigrams and ± 7.2% for perfusion scintigrams. When a second blinded observer made the same calculation on both infarct and perfusion scintigrams in all patients, the two observers agreed within ± 5% in 85% of cases. With greater disagreement, the measurement was repeated jointly and a consensus value was obtained. Figure 1 shows infarct and perfusion scintigrams and their quantitation in a patient with a small scintigraphic infarct. Figure 2 shows a similar assessment in a patient with a large anterolateral infarction.

Equilibrium blood pool scintigrams were performed on the day of the onset of symptoms in 14 patients (25.5%), 2–4 days thereafter in 34 patients (61.8%), and within 10 days in all patients. In the first 22 patients, 99mTc albumin34 was administered, and in the rest, in vivo labeled red blood cells35 were used. In our first 18 patients, blood pool scintigrams were performed in the dual-gated mode to a total of 800,000 counts acquired in 40-msec end-diastolic and end-systolic frames in 30° RAO and 60° LAO projections. In these studies, LVEF was calculated by the biplane geometric formula of Sandler and Dodge36 applied to the end-diastolic and end-systolic left ventricular perimeter outlines taken from transparencies of the gated images. In the last 40 studies, blood pool scintigraphy was performed using multiple-gated scintigraphy, with the acquisition of 29 frames to a total of 4,500,000 counts in the 30° RAO and “best septal” LAO projections. The latter was performed with a 15° caudal tilt and was chosen from a number of ungated LAO images that best separated the ventricles. All multiple-gated studies were acquired on a PDP 11/40 computer and LVEF was calculated by counts data obtained from

![Figure 1. Scintigraphic sizing of a small acute myocardial infarction. (top) Technetium-99m pyrophosphate (PYP) scintigrams. (center) Thallium-201 (TI-201) myocardial perfusion scintigrams. (bottom) The abnormal technetium area is outlined. The perfusion image abnormality is similarly identified and expressed as an absolute abnormality and as a percentage of the projected left ventricular myocardium. ANT = anterior; LAO = left anterior oblique; LLAT = left lateral.](http://circ.ahajournals.org/content/66/5/962/full)}
left ventricular regions of interest identified on end-diastolic and end-systolic frames viewed in a 128 × 128 matrix on a high-quality DeAnza display. Using a paraventricular end-systolic background region of interest, LVEF was determined in these studies in the conventional way by dividing the background-corrected stroke counts by the background-corrected end-diastolic counts. We have documented an excellent correlation between LVEF established at contrast ventriculography and scintigraphic LVEF calculated by both geometric37 and counts38 methods. Both methods yield a normal LVEF of ≥ 55%, with an interobserver variation of ± 4%.

Clinical Course and Follow-up

Five patients died during the initial hospitalization. Fifty-seven patients survived the acute phase and were followed for an average of 16 ± 10 months (± sd) (range 10 days to 34 months). Six patients underwent coronary artery bypass graft surgery due to persistent angina 10 days to 14 months after their infarction and were considered to end their follow-up period at that time. Forty-two of the 57 acute survivors were followed after discharge in the cardiac clinic, while the remainder were returned to the care of their referring cardiologist or internist. Patients and their physicians were contacted every 3 months to establish survival and to determine the symptomatic state. Specific interest was taken in the presence of angina, defined as stress-related chest pain, or the equivalent, or CHF. The latter was indicated by the development of exertional dyspnea, shortness of breath, or easy fatiguability. These findings were always supported by central or peripheral findings on physical examination, including neck vein distention, pulmonary rales, gallop rhythm, evidence of cardiomegaly, hepatomegaly or edema, and by radiographic evidence of pulmonary congestion. Both angina and CHF were assessed according to the criteria of the New York Association.39 Patients were divided into groups by their status during follow-up: an asymptomatic group (ASX), which included patients who presented no symptoms that required treatment; an angina group (ANG), which included patients who reported only angina and required treatment but showed no evidence of CHF; a CHF group, which included patients who presented symptoms or signs of CHF requiring treatment regardless of the presence or absence of angina; and a group of patients who died of cardiac causes (DCC), which included those who died as a consequence of their infarct during hospitalization as well as those who died during follow-up. Deaths outside the hospital were considered due to cardiac causes if they were recorded as such by the patient’s physician, or occurred suddenly (within 6 hours after the onset of symptoms). Among the six patients who underwent coronary artery bypass graft surgery, five were from the ANG and one was from the CHF groups.

Data Analysis

To determine the prognostic value of scintigraphic indicators obtained during the initial hospitalization

FIGURE 2. Scintigraphic sizing of a large acute myocardial infarction. Format and abbreviations are as in figure 1.
for AMI with respect to long-term clinical course, individual quantitative data from Tc-PYP infarct scintigrams, $^{201}$TI perfusion scintigrams and blood pool scintigrams were consolidated according to the clinical group. Mean values and standard deviations for scintigraphic infarct size, perfusion abnormalities and left ventricular ejection fractions were calculated for the DCC group and for patients who survived at the time of last follow-up and, among the latter, for the ASX, ANG and CHF groups.

Quantitative differences in the size of scintigraphic abnormalities were analyzed by means of a one-way, nonweighted means analysis of variance. The between-groups variations were partitioned using planned orthogonal comparisons. In addition, to compare all possible pairs of groups, a Student-Newman-Keuls test was conducted. The scintigraphic indicators thus identified to be significantly different between groups were further analyzed by establishing breakpoint values that could be used to prospectively classify patients into those groups. Initial breakpoint values were those which, for each scintigraphic parameter, yielded the optimal detection of patients who died. With breakpoint levels determined in this manner, each indicator was tested for accuracy of prediction of death or survival, and development or absence of symptoms. Additional specific breakpoint values were sought that could better separate symptomatic subgroups. Since death and the development of heart failure may be considered poorer clinical outcomes than the absence of symptoms or the development of reversible angina, each indicator was tested for the accuracy of classification of patients who had a favorable evolution (ASX or ANG) vs an unfavorable evolution (CHF or DCC). To determine the effect of the time of imaging after the event to the related image findings, the scintigraphic infarct and perfusion abnormalities and LVEF were analyzed according to the time of study after infarction in all study patients. Student-Newman-Keuls multiple-comparison tests were applied to temporal groups of scintigrams obtained within 24 hours after symptoms onset, 2–4 days after onset, and 5–10 days after the event. Many of the values reported are followed by their standard deviations.

### Results

Among the 62 patients, 49 had electrocardiographic evidence of transmural infarction and 12 of subendocardial infarction. In one patient with two previous infarcts, the nature and location of the acute event could not be determined. Among the 49 patients with transmural infarction, 20 (41%) had anterior, four (8%) lateral and 25 (51%) inferior infarctions. Among those with subendocardial infarction, seven (58%) had anterior, two (17%) lateral and three (25%) inferior infarctions. Thirteen patients among the population manifested congestive heart failure during the initial hospitalization.

#### Clinical Outcome

Seventeen patients (27.4%) died of cardiac causes; they constituted the DCC group. Five of these patients died during the initial hospitalization and 12 after discharge, 11 of them within the first year after their AMI. Twenty-one patients (33.9%) constituted the ASX group and were asymptomatic at the time of discharge, remaining so during the follow-up period, which lasted a mean of 16.4 ± 9.6 months. Twenty-four patients (38.7%) presented cardiac symptoms after discharge: 10 (16.1%), the ANG group, developed angina during the mean follow-up period of 10 (± 10.3 months) and 14 (22.6%), the CHF group, developed CHF during the mean follow-up period of 18.2 ± 9.5 months. The duration of the follow-up periods in the ASX, ANG and CHF groups were not statistically different.

Table 1 presents the predictive accuracy related to the presence or absence of a variety of clinical variables noted at the time of admission. Although transmural infarction and anterior location were related to a somewhat higher incidence of CHF and death on follow-up (51% and 56%, respectively) than subendocardial infarction and inferior location, these bore no significant relationship to the late clinical outcome.

### Table 1. Predictive Accuracy of Postinfarct Prognosis from Clinical Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>TM (n = 49)</th>
<th>SEI (n = 12)</th>
<th>Ant (n = 27)</th>
<th>Inf (n = 28)</th>
<th>Prior MI (n = 22)</th>
<th>No prior MI (n = 40)</th>
<th>CHF (n = 13)</th>
<th>Uncomplicated (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For an asymptomatic course (n = 21)</td>
<td>33</td>
<td>42</td>
<td>34</td>
<td>34</td>
<td>23</td>
<td>40</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>For a favorable prognosis (n = 31)</td>
<td>49</td>
<td>58</td>
<td>44</td>
<td>58</td>
<td>36</td>
<td>57</td>
<td>17</td>
<td>79</td>
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<tr>
<td>For CHF (n = 14)</td>
<td>20</td>
<td>25</td>
<td>28</td>
<td>14</td>
<td>37</td>
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<tr>
<td>For death (n = 17)</td>
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<td>28</td>
<td>27</td>
<td>28</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>For an unfavorable prognosis (n = 31)</td>
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<td>42</td>
<td>56</td>
<td>42</td>
<td>64</td>
<td>43</td>
<td>83</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviations: Ant = anterior infarction; CHF = congestive heart failure during acute hospitalization; Inf = inferior infarction; MI = myocardial infarction; SEI = subendocardial infarction; TM = transmural infarction; Uncomplicated = without CHF or rhythm or conduction abnormality during acute hospitalization.
Twenty-two patients studied had evidence of prior infarction. Overall, patients with prior infarction had a worse prognosis than those without prior infarction: 14 of 22 patients developed CHF or died, while only 17 among 40 patients without prior infarction had these outcomes ($p < 0.05$). Also, among 31 patients who were asymptomatic or had angina on late follow-up, eight had prior infarction, while 14 of 31 patients who had CHF or death on late follow-up also had prior infarction. Among 13 patients who presented acutely with evidence of heart failure, seven (54%) died and 11 of these 13 (83%) either died or needed treatment for CHF during follow-up. While this incidence of death among those presenting initially with evidence of heart failure was significantly higher than the incidence of death among those presenting without evidence of heart failure (54% vs 20%, $p < 0.05$), 10 of 49 patients (20%) without initial evidence of heart failure developed CHF. Thus, 40% of those presenting without evidence of failure developed either CHF or died. The presence of atrial arrhythmias, ventricular arrhythmias or conduction abnormalities as seen in 25 patients was related to a poor prognosis and a high incidence of CHF (21%) and death (32%).

While patients in the DCC group had significantly larger values for peak serum CK-MB than those in the ASX group ($253 \pm 211 \text{ IU vs } 113 \pm 130 \text{ IU}, p < 0.05$), peak CK-MB values could not differentiate either group from those in the CHF group. While a peak serum CK-MB value of $\geq 100 \text{ IU}$ identified 13 of 17 patients (76%) in the DCC group, these levels were also present in 19 of 45 (40%) survivors — in 12 of 31 (39%) of those without CHF and in seven of 21 (33%) in the ASX group.

### Scintigraphic Parameters of Infarct Size

Forty-eight of the 57 (82.5%) $^{99m}$Tc-PYP studies were positive. Four of 12 patients (33%) with subendocardial infarcts had negative $^{99m}$Tc-PYP scintigrams and five of 45 (11%) with transmural infarcts had negative scintigrams, imaged a mean of 2.3 days after the onset of symptoms. Only one of the 48 perfusion scintigrams was negative. Imaging in this case was performed on the day after the onset of symptoms. Among 13 $^{201}$TI perfusion scintigrams performed in patients with prior infarction, 11 (84.6%) demonstrated perfusion abnormalities in regions different from the location of acute necrosis as determined by the ECG. In six of these 11, where preexisting electrocardiographic Q waves were present, the additional perfusion defects corresponded to the area of old infarction.

The average perfusion abnormality in three projections was always at least 10% lower than the largest measured perfusion defect. While the average perfusion scintigraphic abnormality and the largest measured abnormality could differentiate the ASX group from the DCC group, only the largest projected abnormalities could differentiate among survivor prognostic subgroups. Table 2 shows the mean values obtained for quantitative measures of $^{99m}$Tc-PYP scintigraphic infarct size, scintigraphic perfusion abnormality and LVEF in 22 patients with and 40 patients without prior infarction for each prognostic subgroup. Although more patients with prior infarction had larger scintigraphic abnormalities, there was no significant difference between scintigraphic indicators in patients with and without prior infarction as a whole or between patients with and without prior infarction in each follow-up group. When the acquired scintigraphic studies were analyzed with respect to their time of acquisition after infarction, there were also no significant differences related simply to the time of imaging.

### Scintigraphic Parameters and Mortality

Quantitative scintigraphic values were compared in survivors and nonsurvivors and the results are shown in figure 3 and table 3. All scintigraphic values distinguished patients according to late mortality. The abso-

<table>
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<tr>
<th>Group</th>
<th>Prior MI</th>
<th>n</th>
<th>$^{99m}$Tc-PYP (cm$^3$)</th>
<th>$^{201}$TI (cm$^3$)</th>
<th>$^{201}$TI (%)</th>
<th>$^{201}$TI (%)</th>
<th>LVEF (%)</th>
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<tbody>
<tr>
<td>ASX</td>
<td>No</td>
<td>16</td>
<td>19.7 ± 10.9</td>
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<td>9.3 ± 4.2</td>
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<td>5</td>
<td>6.3 ± 3.2</td>
<td>9.6 ± 2.3</td>
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<td>ANG</td>
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<td>23.1 ± 5.6</td>
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<td>28.7 ± 19.9</td>
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<td>26.2</td>
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<td>6</td>
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<td>29.5</td>
<td>22.4</td>
<td>41.5</td>
<td>33.4</td>
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Abbreviations: ASX = asymptomatic; ANG = angina; CHF = congestive heart failure; DCC = died of cardiac causes; MI = myocardial infarction; LVEF = left ventricular ejection fraction.
lute areas of largest $^{99m}$Tc-PYP and largest perfusion abnormality were significantly greater in patients who died than in survivors. The percent perfusion abnormality and average perfusion abnormality values were also significantly higher in nonsurvivors, while LVEF was significantly lower.

To further evaluate their discriminating power, individual values obtained for each indicator were plotted for survivors and nonsurvivors (fig. 4) and breakpoint values were selected that optimized detection of deaths without undue loss of overall accuracy. Correct classification rates were defined as the number of patients correctly classified in prognostic subgroups by the test result divided by the total number of patients classified using the given test. These were calculated as percentages of dead and surviving patients who could be selected by each indicator using its related breakpoint value. Similarly, the positive or negative predictive accuracies of scintigraphic values were defined as the percentage of scintigraphic studies with a given range of abnormalities, above or below the breakpoint value, that correctly classified a patient in a given prognostic subgroup. Overall, a percentage perfusion abnormality $\geq 35\%$ correctly classified, to subsequent survival or death, $81.2\%$ of patients, while an absolute $^{99m}$Tc-PYP infarct size of $\geq 25$ $cm^2$ correctly classified $77.2\%$. An absolute perfusion abnormality of $\geq 20$ $cm^2$ correctly identified $70.8\%$, and an LVEF $\geq 52\%$ correctly classified $54.6\%$ of patients. Average values of perfusion abnormalities in multiple projections yielded somewhat lower values than comparable largest measured perfusion defects. Correct classification of deaths ranged from $76.9\%$ for average perfusion values to $92.9\%$ for LVEF, while correct classification of survival ranged from $41.5\%$ for LVEF to $80\%$ for the largest measured perfusion abnormality. All scintigraphic values demonstrating abnormalities less extensive than their breakpoint values predicted survival in most patients and provided a high negative predictive accuracy for death, always greater than $87\%$. The positive predictive accuracy of a scintigraphic parameter more than the related breakpoint value was lower. A percent perfusion abnormality of $\geq 35\%$ predicted death in $61\%$ of cases. Survival curves for $^{99m}$Tc-PYP infarct size $\geq 25$ $cm^2$ and for percent perfusion abnormality $\geq 35\%$ are shown in figure 5.

**Scintigraphic Parameters and Morbidity**

Figure 6 is a comparison of the mean values for each scintigraphic measurement in each of the three follow-up groups in surviving patients. Average values of perfusion abnormalities could not discriminate among surviving subgroups and thus were no longer evaluated. Quantitative values for both largest measured absolute and percent perfusion abnormalities and LVEF in the ASX group were significantly different from the values in patients of the CHF group, but were not significantly different from the ANG group. However, the absolute perfusion abnormality and LVEF were significantly different in the ANG group compared with the CHF group. The $^{99m}$Tc-PYP infarct area was not significantly different in any of the groups, al-

**TABLE 3. Prediction of Mortality and Survival After Acute Myocardial Infarction by Scintigraphic Indicators**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>n</th>
<th>No. of deaths</th>
<th>Survivors — correct classification</th>
<th>Non-survivors — correct classification</th>
<th>Overall correct rate</th>
<th>Positive predictive accuracy</th>
<th>Negative predictive accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest $^{99m}$Tc-PYP ($\geq 25$ $cm^2$)*</td>
<td>57</td>
<td>15</td>
<td>80.0%</td>
<td>76.2%</td>
<td>77.2%</td>
<td>57% (12/21)</td>
<td>92% (33/36)</td>
</tr>
<tr>
<td>Average $^{201}$TI ($\geq 12$ $cm^2$)$^+$</td>
<td>48</td>
<td>13</td>
<td>76.9%</td>
<td>57.2%</td>
<td>63.3%</td>
<td>40% (10/25)</td>
<td>87% (20/23)</td>
</tr>
<tr>
<td>Largest $^{201}$TI ($\geq 20$ $cm^2$)$^+$</td>
<td>48</td>
<td>13</td>
<td>92.3%</td>
<td>62.9%</td>
<td>70.8%</td>
<td>48% (12/25)</td>
<td>92% (21/23)</td>
</tr>
<tr>
<td>Average $^{201}$TI ($\geq 21%$)$^+$</td>
<td>48</td>
<td>13</td>
<td>76.9%</td>
<td>74.2%</td>
<td>75.1%</td>
<td>53% (10/19)</td>
<td>90% (26/29)</td>
</tr>
<tr>
<td>Largest $^{201}$TI ($\geq 35%$)$^+$</td>
<td>48</td>
<td>13</td>
<td>84.6%</td>
<td>80.0%</td>
<td>81.2%</td>
<td>61% (11/18)</td>
<td>93% (28/30)</td>
</tr>
<tr>
<td>LVEF ($\leq 52%$)</td>
<td>55</td>
<td>14</td>
<td>92.9%</td>
<td>41.5%</td>
<td>54.6%</td>
<td>35% (13/37)</td>
<td>94% (17/18)</td>
</tr>
</tbody>
</table>

*Including nine negative studies.
†Including one negative study.
*Abbreviation: LVEF = left ventricular ejection fraction.
though the mean value in the ASX group (17.6 ± 2 cm²) was lower than that seen in both the ANG (23.1 ± 9.7 cm²) and the CHF groups (29.7 ± 13.9 cm²).

Since quantitative scintigraphic values were not significantly different in asymptomatic and angina patients, both groups were consolidated to evaluate the discriminating power of each indicator for separating surviving patients who did not develop heart failure from the CHF group. Individual values for each measurement are plotted with respect to the presence or absence of CHF in figure 7. Classification rates were calculated first using the same breakpoint values chosen for the analysis of mortality. Overall correct classification rates were 73.8% for Tc-PYP infarct abnormalities ≥ 25 cm², 74.3% for absolute perfusion abnormality ≥ 20 cm², 68.6% for percentage perfusion abnormality ≥ 35%, and 61% for LVEF ≥ 52%. Correct classification of CHF patients ranged from

**Figure 4.** Individual scintigraphic values of survivors and nonsurvivors. Absolute perfusion (TI-201) image abnormalities of 20 cm², or 35%, technetium-99m pyrophosphate (Tc-PYP) infarct size of 25 cm² and an ejection fraction (EF) of 52% best separated survivors from nonsurvivors.

**Figure 5.** Survival changes. (top) Survival curves for patients with scintigraphic technetium-99m pyrophosphate (PYP) image infarct size < 25 cm² and ≥ 25 cm². (bottom) Survival curves for perfusion image abnormalities < 35% and ≥ 35% of the projected left ventricular area. The latter was best able to separate these subgroups of late prognosis in the immediate postinfarction period.

**Figure 6.** Quantitative scintigraphic values in the asymptomatic (ASX), angina (ANG) and congestive heart failure (CHF) groups. The absolute perfusion abnormality and left ventricular ejection fraction (LVEF) best differentiated between groups. No scintigraphic variable could differentiate between the ASX and ANG groups. *p < 0.05. TI-201 = thallium-201; PYP = technetium-99m pyrophosphate.
46.1% for the absolute $^{99m}$Tc-PYP abnormality to 78.5% for the LVEF, while correct classification of patients who did not develop CHF ranged from 48.1% for LVEF to 87.0% for the percent perfusion abnormality. Again, positive predictive values for the development of CHF were not as high as the negative predictive values of scintigraphic measurements. A perfusion abnormality $\geq 20$ cm$^2$ predicted the development of CHF in survivors with an accuracy of 61%, while a value of less than 20 cm$^2$ predicted the absence of CHF with an accuracy of 81%. Further assessment showed no advantage of other breakpoint values with reference to infarct or perfusion abnormalities, but a LVEF $\leq 42\%$ appeared more specific for the identification of surviving patients with CHF. An LVEF of $\leq 42\%$ correctly classified 85% of surviving patients with regard to CHF while all patients with LVEF $\leq 42\%$ had CHF and all patients not manifesting CHF had EF $\geq 42\%$. However, only 57% of patients with CHF had an LVEF $\leq 42\%$ (table 4).

The discriminating power of these same breakpoint values for separating patients who had unfavorable evolution, including those in the DCC and CHF groups, and those who had a favorable evolution, including those in the ASX and ANG groups, is shown in table 5. All scintigraphic variables had correct classification rates above 69%. The best scintigraphic study for selection of patients into favorable and unfavorable prognostic groups was the absolute size of the scintigraphic perfusion abnormality. Eighty percent of pa-

![Figure 7](image_url)

**Figure 7.** Individual scintigraphic values of patients with congestive heart failure (CHF) and those without CHF. Overall, the size of the absolute perfusion abnormality best separated these groups. Tl-201 = thallium-201; Tc-PYP = technetium-99m pyrophosphate; EF = ejection fraction.

**Table 4.** Prediction of Congestive Heart Failure After Acute Myocardial Infarction by Scintigraphic Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>CHF</th>
<th>No CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc-PYP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>((\geq 25) cm$^2$)*</td>
<td>42</td>
<td>29</td>
</tr>
<tr>
<td>$^{201}$Tl ((\geq 20) cm$^2$)†</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>$^{201}$Tl ((\geq 35%))†</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>LVEF ((\leq 52%))</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>LVEF ((\leq 42%))</td>
<td>41</td>
<td>27</td>
</tr>
</tbody>
</table>

*Including nine negative studies.
†Including one negative study.

Abbreviations: CHF = congestive heart failure; LVEF = left ventricular ejection fraction.
patients with perfusion defects $\geq 20 \text{ cm}^2$ had an unfavorable evolution and 78.3% of patients with perfusion defects $\leq 20 \text{ cm}^2$ had a favorable evolution. Similarly, this variable provided both positive and negative predictive values of 77% for the development of an unfavorable evolution, while an LVEF $\leq 42\%$ had a perfect positive predictive accuracy. There were at least two scintigraphic variables with abnormalities beyond their breakpoint value in every patient with an unfavorable prognosis, but this was also seen in some patients with a favorable prognosis. The added value of multiple scintigraphic parameters could not be accurately assessed, since each study was not performed in all patients.

**Discussion**

The results of our study suggest that quantitative values of scintigraphic infarct size, perfusion deficit and LVEF determined early after the event provide excellent prognostic information regarding the long-term clinical course, superior for the group as a whole to any other tested, clinical or laboratory parameter. The largest projected scintigraphic infarct abnormality correlates best with pathologic infarct size in animals and relates best to prognosis in patients. In other studies, we have assessed scintigraphic infarct and perfusion image abnormalities in terms of both the mean of projected abnormalities and the largest projected abnormality. The areas of well-perfused myocardium lying in front of or behind abnormal zones might obscure the full extent of perfusion abnormality and lead to an underestimation. Possibly for this reason, the largest projected perfusion abnormality, expressed in both absolute terms and as a percentage of projected left ventricular area, provided a more accurate prognostic measure than did the average perfusion abnormality.

Quantitative computer methods are useful, add to interpretive objectivity, may add to diagnostic accuracy and have been used to quantify variables related to scintigraphic infarct size. Owing to the starting date of this study, which was before the establishment of quantitative techniques, computer methods were not applied to the sizing of the area or density of abnormalities on $^{99m}$Tc-PYP or perfusion scintigrams. Although computer methods allow an accurate assessment of scintigraphic defect size, it would be much simpler and less expensive if scintigraphic variables could be reliably assessed in analog form by visual methods. These methods appear to be reproducible in the current study and support the findings of Silverman and Wackers and co-workers, who documented the close agreement between visual and computer assessment of scintigraphic perfusion abnormalities early after infarction. Other investigators have used similar planimetric methods to measure scintigraphic abnormalities after infarction and documented their reproducibility. As in prior studies, we have shown that infarct and perfusion scintigraphy performed early after AMI provide an excellent profile of late prognosis. While all scintigraphic studies were obtained during the acute hospitalization, unlike the study of Silverman and co-workers, scintigraphic studies were often obtained days after the event. While such delay influences scintigraphic infarct size and, particularly, the size of the perfusion abnormality, Silverman and co-workers found no relationship between time of perfusion scintigraphy and defect size. Similarly, Wackers and co-workers have shown a correlation between scintigraphic perfusion abnormalities and pathologic infarct size that appeared little influenced by temporal factors. In the current study, there was no significant difference in either the size or the prognostic significance of measured scintigraphic abnormalities performed at varying intervals after the time of acute infarction.

Although patients with transmural and anterior infarction had a slightly poorer prognosis, patient age, sex, and site of acute infarction bore no relationship to the eventual late prognosis. Since scintigraphic defect size was related to prognosis after AMI, it was not surprising that there was no significant difference between scintigraphic abnormalities in those with and those without prior infarction within diagnostic prognostic subgroups. Although more patients with prior infarction had larger abnormalities and a poorer prog-

### Table 5. Prediction of Favorable or Unfavorable Evolution after Acute Myocardial Infarction by Scintigraphic Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Unfavorable evolution</th>
<th>Favorable evolution</th>
<th>Overall correct classification rate</th>
<th>Positive predictive accuracy</th>
<th>Negative predictive accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc-PYP</td>
<td>$\geq 25 \text{ cm}^2$</td>
<td>57 28</td>
<td>64.3%</td>
<td>29 86.2%</td>
<td>75.4%</td>
</tr>
<tr>
<td>$^{201}$TI</td>
<td>$\geq 25 \text{ cm}^2$</td>
<td>48 25</td>
<td>80.0%</td>
<td>23 78.3%</td>
<td>79.2%</td>
</tr>
<tr>
<td>$^{201}$TI</td>
<td>$\geq 35%$</td>
<td>48 25</td>
<td>60.0%</td>
<td>23 87.0%</td>
<td>72.9%</td>
</tr>
<tr>
<td>LVEF $\leq 52%$</td>
<td></td>
<td>55 28</td>
<td>85.7%</td>
<td>27 51.9%</td>
<td>69.1%</td>
</tr>
<tr>
<td>LVEF $\leq 42%$</td>
<td></td>
<td>55 28</td>
<td>57.1%</td>
<td>27 100.0%</td>
<td>78.2%</td>
</tr>
</tbody>
</table>

*Including nine negative studies.
†Including one negative study.
Abbreviation: LVEF = left ventricular ejection fraction.
nosis than patients without prior infarction, there was also no difference in the size of scintigraphic abnormalities between those with and without prior infarction (table 2). Patients with arrhythmias and conduction abnormalities also demonstrated a high incidence of CHF or death, but few patients so presented. While patients presenting acutely with CHF demonstrated a greater incidence of CHF and death, many patients who did not present with CHF early went on to develop it or died.

When performed and analyzed in the manner described, all scintigraphic indicators seemed adequate to separate survivors from nonsurvivors. The most accurate separation between late survivors and those who died was provided by the perfusion abnormality, expressed as the percentage of projected left ventricular area, with an overall correct classification of 81.2%, a positive predictive accuracy of 61%, and a negative predictive accuracy of 93%. A value of 35% best separated these groups and corresponds closely to the percentage of left ventricular mass that has been noted to be infarcted in prior pathologic studies in patients succumbing to the acute event. An absolute scintigraphic perfusion abnormality of $\geq 20$ cm$^2$ also accurately identified patients who died late with a 92% accuracy. A scintigraphic LVEF $\leq 52\%$ measured early after the event was seen in 93% of patients who died, but was also seen in 58% of patients who survived, and provided a positive predictive accuracy for death of only 35% (table 3). The negative predictive accuracy of scintigraphic measurements was generally greater than their positive predictive accuracy. We can be more certain that a patient will not develop CHF or die if quantitative scintigraphic values are less abnormal than the related breakpoint value than we can that a patient will develop CHF or die if these parameters are more abnormal than the breakpoint value. Since the positive predictive accuracy for patients with large scintigraphic abnormalities is somewhat lower than the negative predictive accuracy for those with small scintigraphic abnormalities, the implication can be made that the group with the largest scintigraphic defects and more depressed function is more heterogeneous with their clinical outcome depending to a greater degree on numerous clinical and therapeutic factors that might affect the survival of myocardium in jeopardy. Such a relationship has been established in reference to the LVEF, where a high LVEF early after infarction was related with great reliability to a favorable outcome but a low LVEF was related to a variable prognosis.

Scintigraphic measurements were less effective in discriminating surviving patients according to their clinical course and found particular difficulty in separating asymptomatic patients from those who developed angina. The size of the scintigraphic $^{99m}$Tc-PYP infarct abnormality was larger in patients who developed CHF but could not separate these from asymptomatic patients, possibly owing to the relatively small population size. However, scintigraphic measurements of perfusion and function could separate these groups, suggesting that the occurrence of CHF could be related as much to associated ischemic abnormalities as to the size of the infarct itself. Owing to their relationship to both acute and remote infarction, as well as ongoing ischemia, perfusion defects and LVEF may have specific prognostic advantages. While infarct and perfusion scintigrams could discriminate between patients who developed CHF and all other survivors, the best overall separation between surviving patients who developed CHF and those who did not was, not surprisingly, achieved by measurements of ventricular function (table 4). An LVEF of $\leq 42\%$ identified only 57.1% of CHF patients, but when present, was associated with CHF in all cases.

Combinations of scintigraphic variables did not appear to add prognostic value. However, since each scintigraphic study was not performed in every patient, later studies must assess the incremental prognostic accuracy of multiple scintigraphic parameters.

Part of the prognostic value of a large scintigraphic abnormality relates to an expression of the probable vulnerability of the individual patient to subsequent events. It is likely that the extent of scintigraphic abnormality provided some measure of the reserve capability in each patient; and the larger the initial scintigraphic abnormality in the patient without CHF, the more vulnerable the patient to the development of symptoms.

The value of a reliable prognostic indicator for patients who have suffered an AMI lies in the separation of high-risk patients who may benefit from alternative therapy. In this context, patients who are at risk of death or of developing CHF clearly constitute a group apart from patients who will remain asymptomatic or who will develop angina, a favorable evolution. When breakpoint values were applied to the discrimination of patients who had a favorable or an unfavorable evolution, all scintigraphic indicators had a correct classification rate greater than 69% (table 5).

These results support previous reports indicating the potential prognostic significance of scintigraphic measurements of infarct size and related function measured early after the event. While not perfect predictors of prognosis, a variety of scintigraphic measurements appear to have significant late prognostic value and, considering all patients, in this study were superior to all other clinical or laboratory parameters. Although others assessed the density of scintigraphic abnormality as well as its area, current results were determined by a simple area measurement made by visual assessment of analogue images. Although such measurements are somewhat subjective and susceptible to variations related to photographic technique, they demonstrated satisfactory reproducibility by trained observers. Other methods of evaluation using objective computer assessment might add to scintigraphic accuracy. Scintigraphic determinations are safe, noninvasive, relatively inexpensive and can provide useful information with a single determination. While one may provide an accurate prognosis in the patient presenting after infarction with evidence of severe CHF or shock, it is not easy to predict the course of individual patients presenting with uncom-
licated infarction, minimal evidence of pulmonary congestion or arrhythmia. It was particularly this latter population that we studied, and in this population scintigraphic estimate of prognosis would be of greatest value. Further study is required before optimal scintigraphic values of acute infarction size can be established and applied clinically to guide treatment in the individual infarct patient.

References

The late prognostic value of acute scintigraphic measurement of myocardial infarction size.

J Perez-Gonzalez, E H Botvinick, R Dunn, S Rahimtooia, T Ports, K Chatterjee and W W Parmley

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